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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)

TEVE-121US

Application Number

10/646,361

Filed

August 21, 2003

First Named Inventor

Xian-Ming Zeng

Art Unit

1616

Examiner

**James Henry Alstrum
Acevedo**

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).

Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.☐ assignee of record of the entire interest.See 37 CFR 3.7.1 Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)☒ attorney or agent of record.Registration number **33,243**☐ attorney or agent acting under 37 CFR 1.34.

Registration number if acting under 37 CFR 1.34 _____


Signature**Stephen D. Harper**

Typed or printed name

610-407-0700

Telephone number

August 11, 2011

Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.



*Total of _____ forms are submitted

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Reasons for Pre-Appeal Brief Request for Review

Applicants note that the Office Action made errors in law and/or in fact, as explained below. Applicants also, to the extent permissible in a pre-appeal brief, incorporate herein by reference the entire remarks in the previous response dated April 4, 2011

1. Clear Factual Deficiency of Rejection under 35 USC 103(a)

A proper obviousness analysis is by its nature, fact intensive. See, e.g., MPEP 2116.01; stating "As noted in *Brouwer*, 77 F.3d at 425, 37 USPQ2d at 1666, the inquiry as to whether a claimed invention would have been obvious is 'highly fact-specific by design.'" The obviousness analysis in the May 12, 2011, Office Action was factually deficient, for example, in its characterization of the cited references and the differences between the claims and the teaching of the cited references. For example, the rejection stated at the bottom of page 5:

*Ascertainment of the Difference Between Scope the Prior Art and the Claims
(MPEP §2141.012)*

Keller lacks the teaching of carrier particles having a volume median diameter ranging between 70-120 microns. This deficiency is cured by Ward.

The Office Action (e.g., at the top of page 6) indicated that the obviousness analysis therein relied on a finding of motivation that was based on this error of fact; stating, for example:

A person of ordinary skill in the art would have been motivated to make a dry powder formulation comprising lactose particles having a volume median diameter ranging between 70 and 120 microns because it is known in the art that dry powder inhalation formulations comprising lactose carrier particles having a volume median diameter ranging from preferably about 30 to 300 microns can deliver active compounds to the lungs with a fast acting or rapid onset of effect, as suggested by Ward et al. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make a dry powder formulation with lactose particles having a volume median diameter (VMD) ranging between 70 and 120 microns because it is an obvious VMD range that can be used in the preparation of dry powder formulations for delivery of an active to the lungs.

The primary reference Keller teaches dry powder formulations comprising: an active compound having an inhalable particle size (i.e., a mass median aerodynamic diameter (MMAD)

$\leq 10 \mu\text{M}$; preferably $\leq 5 \mu\text{M}$), and an inactive carrier having a non-inhalable particle size (*i.e.*, a MMAD of 10-500 μM ; preferably $\leq 50\text{-}200 \mu\text{M}$). Keller specifically defined "carriers" as "pharmacologically inactive substances" as reproduced below from column 7.

For the exact volumetric dosage of most active compounds or formulations, dilution of the active compound with a pharmaceutically inactive excipient is necessary in order to obtain a dosable unit amount meeting the demands on dosage accuracy. For this purpose, the microfine, inhalable active compound particles are mixed with pharmacologically inactive substances (carriers). The dilution is cho-

As previously discussed, Keller's particle sizes were disclosed in terms of the "mass median aerodynamic diameter" (MMAD) and thus are not directly comparable to the particle size terms of volume mean diameter (VMD) recited in the claims. However, notwithstanding this variation in the terms used to quantify the particle size ranges, Ward cannot cure the deficiency of Keller, at least because (a) Ward does not teach formulations containing lactose as a carrier, and (b) Ward affirmatively teaches that lactose carriers have disadvantages that are overcome by using an active carrier.

A. Ward does not teach formulations containing lactose as a carrier

Ward teaches formulations that simply do not contain any lactose. Instead, Ward's formulations contain both small and large particles of an active drug compound. The larger particles of Ward's active drug compound serve as a carrier, and they also provide an additional amount of the active drug compound that is delivered via the gastrointestinal route. Ward provides a clear rationale for the use of the active compound as its own carrier, *e.g.*, at column 2, lines 32-42:

35 In a second aspect of the invention, upon inhalation, the microfine particles and carrier particles are separated, preferably through input of mechanical or electrical energy. The microfine particles travel through the throat and pass into the lungs. The carrier particles pass into the throat, and are swallowed. Accordingly, active pharmaceuticals are delivered to both the lungs (for a rapid onset or fast acting effect) and to the GI tract (for a slower onset or a more sustained effect).
40 The swallowed dose is preferably at least 10 times greater in weight than the inhaled dose, and preferably is at least 50, 100, or even 1,000 times greater.

B. Ward teaches that disadvantages of lactose carriers are overcome by using an active carrier

Ward's teaching regarding this element is not limited to a simple lack of teaching of lactose as a carrier. Rather, Ward also affirmatively teaches that using the active carriers disclosed in

the reference serves to overcome significant disadvantages of using lactose, e.g., at the bottom of column 2, continuing to column 3 (as reproduced below).

Consequently, in this embodiment, the active carrier particles carry the microfine particles, in much the same way as an excipient, such as e.g.,
65 lactose in conventional formulations. However, since the carrier particles also comprise an active pharmaceutical compound, the disadvantages of using lactose (interactions with the pharmaceutical and/or water vapor) are avoided, while aerosol performance is maintained.

Accordingly, Applicants submit that the obviousness rejection, founded on the premise that the Ward provides teaching that cures the lack of teaching by the primary reference (Keller) *i.e.*, of a mixture of lactose carrier particles with a VMD of 70-120 μm , is factually incorrect.

2. Clear Legal Deficiency of the Obviousness Rejection

The present Office Action finally rejected claims 1-14 as allegedly obvious over Keller (US 6,645,466), in view of Ward (US 6,616,914). As discussed briefly above, the formulations taught by Ward contain no lactose carrier, and Ward's formulations are also specifically taught as overcoming disadvantages associated with formulations containing a lactose carrier. Applicants believe that this raises at least two issues associated with the obviousness analysis: (a) a failure to teach or suggest all elements of the claimed invention, and (b) a failure to provide some reason why the skilled person would modify the prior art in such a way as to obtain the claimed invention.

To support a *prima facie* obviousness rejection, all words in a claim must be considered so that the claimed invention as a whole is compared with the cited references. See, MPEP §§ 2141.02, 2142 and 2143.03. The Board of Patent Appeals and Interferences (BPAI) has confirmed that a proper, post-KSR obviousness determination still requires the Office to make "a searching comparison of the claimed invention – including all its limitations – with the teaching of the prior art." *Ex parte Wada and Murphy*, Appeal 2007-3733, at 7 (BPAI, 2008). Therefore, it remains settled law that a *prima facie* obviousness rejection requires at least a suggestion of all of the claim elements.

The Examination Guidelines of MPEP 2141, Section III provide a series of exemplary rationales that were set out by the US Supreme Court in its holding in *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007). These various rationales, e.g., "combining prior art elements according to known methods to yield predictable results," and "simple substitution of one known element for another to obtain predictable results," are all founded on some finding of

predictability, such that the skilled person would modify or combine elements in the prior art and thereby obtain predictable results, or have a reasonable expectation of success.

Applicants acknowledge that Ward briefly refers (e.g., at column 3, lines 5-12) to conventional formulations that use lactose "generally exceeding the particle size range for inhalable particles (e.g., 1-10 microns)." However, Ward's brief mention that some conventional formulations contain inert carriers such as lactose fails to "cure" the deficiency of the primary cited reference for purposes of an obviousness analysis, unless it provides some reason for the skilled person to modify the teaching of the primary reference in such a way as to arrive at the claimed invention.

For the instant rejection, Ward's teaching would not have provided the skilled person with any motivation to modify the primary reference (Keller) in a way that would generate the claimed invention, or with any guidance in making such a modification, or with any reasonable expectation of success in modifying Keller in such a way as to produce the claimed invention. Rather, Ward provides motivation and expectation of success solely in using the active carrier particles that are taught as curing the deficiencies associated with using lactose carriers, e.g., at the bottom of column 2, continuing to column 3 of Ward (as previously reproduced, above).

Further, Keller and Ward, taken separately or together, fail to teach the required claim elements of:

"a mixture of lactose carrier particles with a VMD of between about 70 and about 120 microns and a diameter of less than 250 microns, wherein up to 96% by weight of the lactose particles are less than 150 microns and wherein up to 25% by weight of the lactose particles are less than 5 microns in diameter."

Thus, even, *arguendo*, were the skilled person (even absent motivation) to modify the teachings of Keller based on the Ward teachings, Applicants' claimed invention would not be the result, at least because the combination of Keller and Ward fails to teach or suggest all the elements of the claimed invention.

Based on the brief discussion above, Applicants respectfully submit that *prima facie* obviousness has not been established over the cited references, commensurate with any of the predictability-based rationales set out in the Supreme Court's *KSR* holding and reiterated in MPEP 2141. Accordingly, Applicants believe that the obviousness analysis underlying the present rejection is legally deficient.

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Pre-Appeal Brief Request for Review Dated: August 11, 2011

Responsive to Office Action of May 12, 2011

3. Conclusion

In light of the foregoing brief discussion of the legal and factual deficiency of the present obviousness rejection, Applicants respectfully submit that all of the pending claims should be allowed.